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Docket No.: 04504/100M693-US2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Samuel P. Sawan et al.

Application No.: 09/617,566 Art Unit: 1616

Filed: July 17, 2000 Examiner: Neil S. Levy

For: CONTACT-KILLING ANTIMICROBIAL DEVICES

DECLARATION BY SAMUEL P. SAWAN UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Samuel P. Sawan declare as follows:

1. I am a citizen of the United States and more than 21 years of age.

2. I am one of the named inventors in this patent application, U.S. Serial No. 09/617,566. A copy of my curriculum vitae is attached as Exhibit A. I have reviewed the pending claims in this application. I make the following declaration in support of this application, for myself and on behalf of my co-inventors.

3. I understand that in the Office Action dated October 23, 2003, the Examiner has rejected claims 25-28, 30-32, 35-36, and 50-55 as anticipated by either Mermel et al. (J Infectious Dis 1993;167:920-4; "Mermel") or U.S. Patent No. 5,019,096 to Fox Jr. et al. ("Fox"), contending that each of these references teach, explicitly or inherently, each and every feature of the claims. In my opinion, however, neither Mermel nor Fox teaches all of the features of the claims, for the

reasons set forth below. In this Declaration, I also describe a comparative experiment between an article of the invention and an article according to the Mermel and Fox references.

Fox and Mermel Do Not Teach Articles With Coatings Comprising the Claimed Components or Having the Claimed Properties

4. Mermel compares the surface antimicrobial activity of some heparin-bonded catheters with a triple-lumen (*i.e.*, "three channel") polyurethane catheter impregnated with chlorhexidine-silver sulfadiazine from Arrow International, Reading, PA (Mermel, page 920-921, bridging paragraph). In contrast to claims 25, 53, and 54, the polyurethane catheter (1) is not a article comprising an adherent antimicrobial *coating*, but an article *impregnated* with antimicrobial compounds, and (2) polyurethane is a *nonionic* polymer, the nitrogens do not become protonated and the carboxyl group does not become anionic (see Figure 1 below). Further, chlorhexidine is not a polymer; (a polymer consists of many, often repetitive subunits, whereas chlorohexidene is a low molecular weight compound; see Figure 2 below). For these reasons alone, the Mermel reference does not teach each and every feature of any of claims 25, 53, and 54.

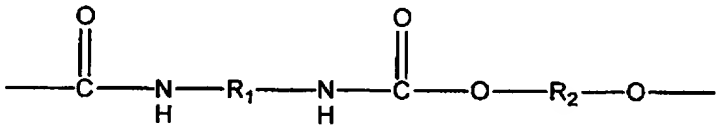


Figure 1. Polyurethane monomer unit wherein R_1 and R_2 is an alkyl or aryl.

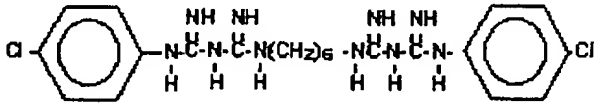


Figure 2. Chlorhexidine

5. The Fox patent describes medical devices and coatings comprising (1) matrix-forming polymers selected from biomedical polyurethane, biomedical silicone, and biodegradable polymers, and (2) antimicrobial agents such as silver salt and chlorhexidine (Fox, Abstract and column 2, lines 9-22). Again, in contrast to claims 25, 53, and 54, the coatings described are not a *polycationic polymer* matrix since polyurethane in itself is not polycationic (see Figure 1), silicone is not polycationic, and chlorhexidine is not a polymer (see Figure 2). Further, a "biodegradable polymer" degrades over time, and is therefore not an *adherent antimicrobial coating* (see Fox, column 11, lines 49-60). For these reasons alone, the Fox patent does not teach each and every feature of any of claims 25, 53, and 54.

6. Both the Mermel reference and the Fox patent only describe articles being impregnated (Mermel) and/or coated (Fox) with materials *releasing biocidal amounts of elutables into the surrounding environment.* This is shown in their so called "Zone of Inhibition" tests (see Mermel, page 921, column 1, 1st full paragraph; and Fox, Example 2 (especially column 17, lines 21-23) and Example 5 (especially column 20, lines 24-29)). Zone of Inhibition tests are standard in the art to evaluate whether a bactericidal component is released from an article, and are basically designed as follows: a portion of the article in question, *e.g.*, a catheter, is embedded into an agar plate which contains nutrients for bacterial growth. The agar plate is then inoculated with bacteria. As the bacteria multiply, they spread across the agar plate, forming bacterial colonies or layers. *If the article releases elutables, these elutables will diffuse across the agar plate. Wherever the concentration of elutables reaches biocidal/bactericidal levels, bacteria will die.* Thus, a "Zone of Inhibition" will form around the article, usually reported as the distance from the article to the outer edge of the inhibition zone.[1]

7. In the Mermel reference, the results of the Zone of Inhibition tests are shown in Table 1 (page 922). For the chlorhexidine-silver sulfadiazine-impregnated polyurethane (Arrow International) catheter, the Zone of Inhibition, *i.e.*, the distance from the catheter where the released elutables reached biocidal levels, ranged between 3.0 and 11.0 mm, depending on which microbe

[1] I understand that a schematic drawing of a Zone of Inhibition test, which might be helpful in this context, has previously been presented in the Response to Office Action filed September 5, 2003.

was tested. In the Fox patent, Zone of Inhibition tests are reported in Example 2, Table 18. For the polyurethane catheters coated with a metallic material and/or chlorhexidine, the Zone of Inhibition ranged from 9 mm to 20 mm. Accordingly, both the Mermel and Fox catheters clearly release biocidal amounts of elutables into the surrounding environment and this release is the basis for the mode of action of the coating technology employed.

Comparative Test

8. ***Comparative Zone of Inhibition Test.*** To further emphasize the differences between the invention and the prior art as represented by the Mermel and Fox references, a comparative Zone of Inhibition test was performed. Briefly, a polyurethane catheter was coated internally and externally with chemically derivatized PHMB and silver iodide using a dip process and was thermally cured to form a crosslinked immobilized the coating on the catheter surface. This catheter, denoted "Surfacine™ catheter", thus represents an article according to the invention. The Zone of Inhibition of *E. coli* bacteria around the Surfacine™ catheter was compared to that of an uncoated polyurethane catheter, denoted "control", and a commercially available polyurethane catheter coated with chlorhexidine and silver sulfadiazine, denoted "Arrowguard Blue®".[2] A product description of the Arrowguard Blue® catheter is attached at Tab 1 (see, especially, page 3, 1st paragraph; and page 4, under the title "Recognized by its blue body..." and footnote number 2). The Arrowguard Blue® catheter is thus representative of a Fox/Mermel type catheter.

9. The results of the comparative Zone of Inhibition test are shown in Figure 3A-3C, attached at Tab 2. The comparative test showed organism growth up to and onto the surface of the control catheter (Fig. 3A), organism growth up to but not on the Surfacine™ catheter (Fig. 3B), and a pronounced Zone of Inhibition around the Arrowguard Blue® catheter (Fig. 3C).[3] The narrow ring around the Surfacine™ catheter represents a layer of one or two cells where bacteria cannot grow or will be killed — that is, bacteria that touch the catheter are killed whereas those just beyond

[2] This test was basically conducted as described in Subramanyam et al. (J Endourology 2000;14:43-48), concurrently submitted in an Information Disclosure Statement.
[3] See, also, Subramanyam et al. (page 46, under "Non-elutability ..." and Figure 5 caption).

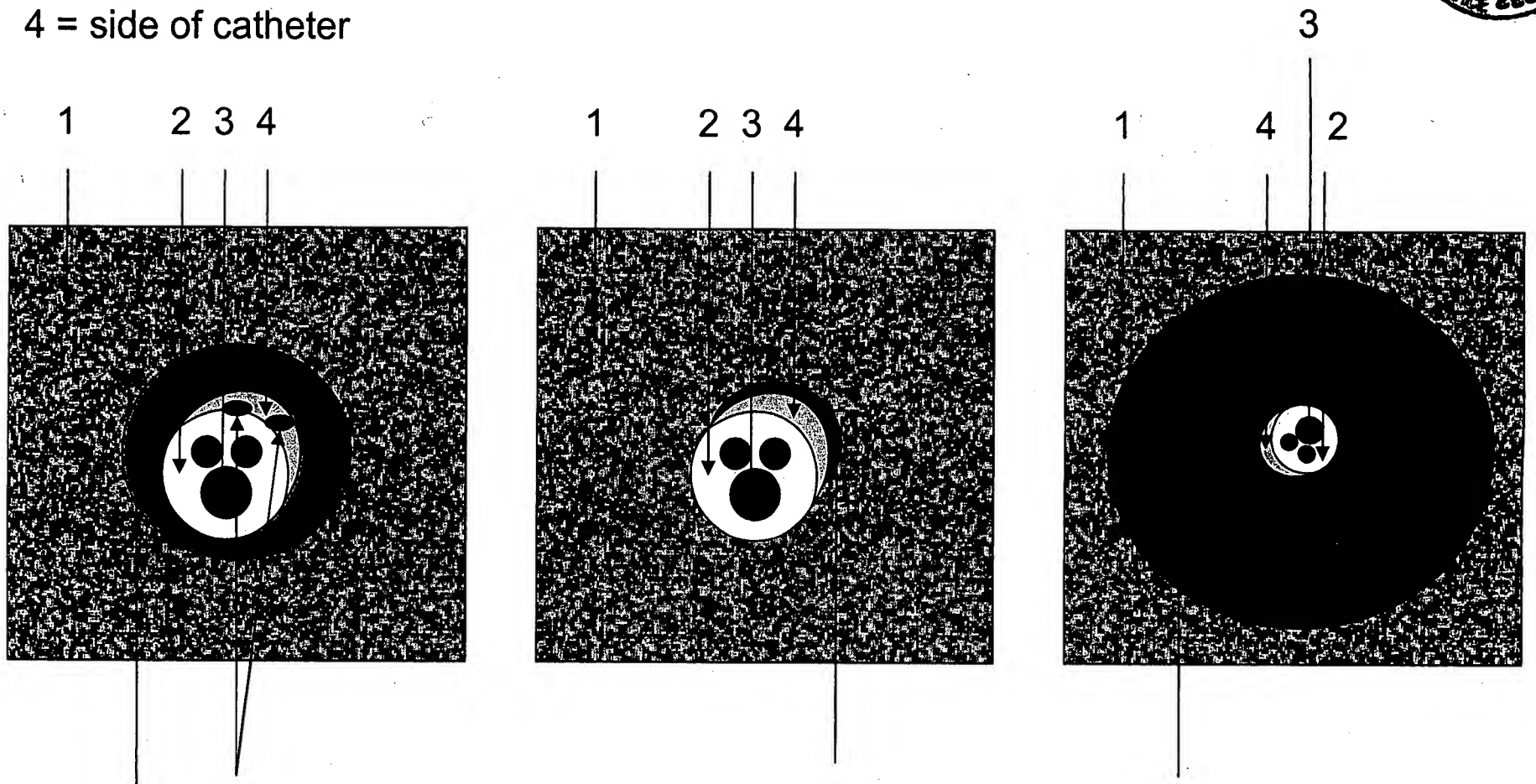
that radius remain viable, hence this persistent "halo" exists that defines the lethality layer. For example, one can stand next to an electric fence at arms length, but touching the electric fence leads to one being electrocuted. Accordingly, this comparison shows that an exemplary article of the invention, in contrast to the Fox/Mermel-type catheters, *does not release biocidal amounts of elutables into the surrounding environment.*

10. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant application or any patent issued thereupon.

Dated: 4-22-04

By: Samuel P. Sawan

1 = bacterial colonies
2 = catheter cross-section
3 = catheter lumen or "channel"
4 = side of catheter



Control ***Surfacine™*** ***ARROWguard Blue™***